maintains that col. 4, lines 19-36; col. 5, lines 50-55; col. 6, lines 12-26; col. 13; and, the claims of **Cummins, Jr.** (U.S. Patent 5,019,382) anticipate claims 1-4 and 6. The Applicant respectfully disagrees.

It is well established in United States patent law that an anticipatory reference under 35 U.S.C. §102 must be enabling to the same degree as an invention seeking patent protection under 35 U.S.C. §112, first paragraph. An analysis of **Cummins** reveals deficiencies with regard to enablement which prevent **Cummins** from anticipating the Applicant's invention. The Applicant's position is supported by two Declarations Under 37 C.F.R. 1.132 submitted previously, specifically the Rule 1.132 Declarations of **Dr. John Lindsey M.D.,** Assistant Professor of Neurology, and **Jerry S. Wolinsky M.D.**, Professor or Neurology. Both Declarants are skilled in the area of autoimmune diseases in general and in multiple sclerosis, diabetes, and rheumatoid arthritis in particular. The Rule 1.132 Declarations support and expand upon the following arguments of the Applicant.

Within Column 4, lines 19-36 of **Cummins**, the disease conditions are listed to which the **Cummins** patent may be directed: ". . . include apparent autoimmune disorders characterized by a chronic tissue degenerative inflammatory condition. Diseases so

characterized include multiple sclerosis, rheumatoid arthritis, stomatitis, and lupus erythematosus." Most of the diseases actually described in the specification of **Cummins** have no autoimmune basis (eg. cancers, acne, warts). Instead, most of the specification and all of the claims describe the treatment of conditions of viral origin. In addition, the vast majority of the conditions in **Cummins** supported by actual clinical data are veterinarian diseases such as canine lupus erythematosus. These points have been addressed by Dr. Wolinsky, who states:

> The experimental database relied upon in the **Cummins** patent is extremely limited. Whereas reasonable information is provided for the treatment of shipping fever in cattle, **Cummins'** additional claims regarding the administration of interferon to treat viral and inflammatory disease are based on pure speculation or limited anecdotal evidence.

The specification of the instant application, in contrast, has targeted a much broader spectrum of autoimmune diseases including 27 cases of multiple sclerosis, four cases of rheumatoid arthritis, and 18 cases of treating autoimmune conditions in animals in which the type one interferon is orally administered and immediately ingested.

Cummins provides only one anecdotal example of the use of interferon treatment in multiple sclerosis. This one anecdotal example, however, is neither conclusive nor enabling. The case involved a 30-year-old Caucasian female who received treatment for

twenty-one days and had no recurrence of neurologic symptoms for nine months. As any clinician can attest, multiple sclerosis is a highly variable disease with unpredictable periods of remission and relapse. Therefore, a single individual having no recurrence of symptoms for nine months is hardly remarkable and certainly not conclusive. In contrast, the instant application contains data from 27 multiple sclerosis patients.

In the office action mailed October 23, 1998, the Examiner states: "A patent cannot be called 'non-enabling' because the applicant has produced data from 27 patients ... versus one example in the patent used." The applicant is not calling the patent "non-enabling" merely because the applicant has produced data from more patients. Rather, the applicant considers the one example given in the patent to be far from conclusive. One skilled in the art would recognize that a nine month remission in multiple sclerosis patent is hardly remarkable given than such a remission is common in untreated multiple sclerosis patients as well. The applicant points out that there are no claims in the **Cummins** patent regarding multiple sclerosis, most likely because the data failed to enable such a claim.

In **Cummins**, a description is given of the treatment of two patients with rheumatoid arthritis with interferon administered through the oral and pharyngeal mucosa. Both were continued on the treatment for 21 days and were described as remaining asymptomatic after treatment. However, **Cummins** fails to define what is meant by asymptomatic. In the specification of current application, in contrast, the treatment of four rheumatoid arthritis patients with ingested interferon is documented in extensive detail. A comprehensive report is made on the results of the clinical tests performed on the four patients. This is lacking in **Cummins,** which thus fails to enable an analysis of the effectiveness of the treatment for rheumatoid arthritis described therein.

Cummins also cites cases of treatment involving malignant lymphoma mesothelioma, and apthous stomatitis which are entirely anecdotal. One having ordinary skill in the art would find these anecdotal examples to be literally incredible and unclear in interpretation of therapeutic efficacy and therefore nonenabling. In fact, this section of Cummins reads more like a marketing tract than a description of a conclusive clinical investigation.

The Applicant's contention that Cummins fails to anticipate the instant invention is substantiated by both Rule 1.132 Declarations. On page 2 of his Declaration, **Dr. Wolinsky** states:

> It is my considered opinion that none of the supporting evidence in **Cummins** is in any way adequate to allow a reasonable physician, i.e. a person with ordinary skill in the art, with a reasonable expectation of being able to successfully utilize oral administration of interferon for the treatment of inflammatory autoimmune disease such as multiple sclerosis, diabetes, and arthritis.

Likewise, **Dr. Lindsey** states on page 6 in his Rule 1.132 Declaration,

> ... the extremely limited clinical anecdotes presented in Cummins would not provide a person with ordinary skill in this art with a reasonable expectation of being able to successfully treat an autoimmune disease such as multiple sclerosis, diabetes, or rheumatoid arthritis by orally administering alpha interferon.

Cummins also fails to anticipate the instant invention because of significant differences in the routes of administration of the interferon. Applicant's claim 1 recites, "A method of treating an auto-immune disease in an animal comprising the step of orally administering a type one interferon such that the type one interferon is ingested immediately upon administration (emphasis added)". This differs considerably from the method of **Cummins** as stated in col. 4, lines 37-43:

> It is critical that the interferon be administered in a dosage form adapted to assure maximum contact of the

> interferon in said dosage form with the oral and pharyngeal mucosa of the human or animal. Contact of interferon can be enhanced by maximizing residence time of the treatment solution in the oral or pharyngeal cavity. Thus, best result seem to be achieved in human patients when the patient is requested to hold said solution of interferon in the mouth for a period of time.

With regards to this issue **Dr. Lindsey** has stated the following in his Rule 1.132 Declaration:

> **Cummins** stressed that contact with the oral or pharyngeal mucosa should be maximized... Clearly, contact with the gastric or intestinal mucosa was regarded as inconsequential, while contact with the oral or pharyngeal mucosa was essential.

Thus, it is clear that the **Cummins, Jr.** patent actually argues against the immediate ingestion of the interferon, actually teaches away from the current application, and certainly does not provide each and every component of the Applicant's claimed methods.

The Examiner has also cited Col. 13 of **Cummins** as anticipating the instant invention. Col. 13 is concerned with the formation of the interferon in the form of lozenges, chewable vitamins, mouthwash, syrup, or effervescent tablet. All of these formulation are designed to maximize contact with the oral and pharyngeal mucosa rather than to facilitate ingestion. For example, in the case of the lozenge, **Cummins** states: "The patient is instructed

to hold the lozenge in his mouth until it is completely dissolved to release the interferon component for contact with the oral mucosa."

In the applicant's animal experiments, animals were fed (implying ingestion) interferon using a 20 gauge ball point needle "placed in the posterior oropharynx (Page 29, line 23)." Such placement results in delivery of the interferon directly to the distal esophagus, stomach and small intestine and bypasses contact with the oral and pharyngeal mucosa. This was verified experimentally by injecting Evan's Blue during routine feeding and sacrifice which confirmed that no contact with the oral or pharyngeal mucosa occurred. Dr. **Wolinsky** states on page 3 of his Declaration, "Convincing data that shows that delivery of the dose of oral interferon must be into the postduodenal small intestine in order to be effective is presented..."

In the applicant's clinical studies with human subjects, the interferon was ingested which allowed brief exposure to the oral mucosa. However, this mucosal contact was minimal unlike in **Cummins** where attempts were made to maximize the contact with the oral and pharyngeal mucosa. This distinction between **Cummins'** method and the instant invention is further noted by **Dr. Lindsey** on page 3 of his declaration:

> In Applicant's clinical studies with human subjects, the interferon was "ingested," which briefly exposed the oral mucosa to the interferon, but no attempts at maximizing contact with the oral mucosa were made not would there have been any significant absorption of the alpha-interferon through the oral or pharyngeal mucosa.

In reference to the applicant's method of administration, Dr. **Wolinsky** states on page 3 of his Declaration, "...this specific route of administration is quite unlike the oral mucosa swish technique described by **Cummins**." In addition, in **Cummins**, the interferon was sometimes discharged from the patient's mouth without ingestion (Col. 12, lines 27-29 of **Cummins**). In contrast, the applicant's specification shows the necessity of interferon interacting with intestinal sites and Peyer's patches.

In the Office action of October 23, 1998, the examiner argues that there is "nothing clearly distinguishable between 'orally administering . . . such that the . . . interferon is ingested after oral administration' and the **Cummins** mode." The distinguishing characteristics have been described in detail *supra*. The Examiner continues "Applicant has argued . . . in his specification . . . that the interferon was fed through a needle inserted into the stomach . . . There are no such limitations in the claims, however, and the relevance of this in view of the instantly claimed limitations is not clear." First of all, it is not the intention of the Applicant that this

was to be the normal mode of administration. Instead, this was done in the animal experiments to assure that the interferon made no oral or pharyngeal contact. It is cited here to prove that the interferon is having its effects through gastric contact rather than through the oral mucosa as in **Cummins**. The relevance of this citation is to demonstrate that the ingested interferon is responsible for the experimental results. The Examiner also argues that the claims do not recite anything to indicate that there is to be only brief exposure of the interferon to the oral mucosa. The claims state that the interferon is to be ingested upon oral administration. This would in of itself imply that the interferon is only in contact with the oral mucosa during the swallowing process, a process which is takes a fairly brief period of time.

Finally, the dosages of interferon used by **Cummins** were smaller than in the instant application. In **Cummins**, the dosages of interferon are given in Col. 4, lines 24-32. These range from 0.01 to 5 I.U./lb. per day. The instant application, in contrast, uses dosages ranging from 5 I.U./kg to about 50,000 I.U./kg (which corresponds to 2.3 I.U./lb. to 23,000 I.U./lb.,), a much greater range than that of **Cummins**. More importantly, as pointed out by Dr. Lindsey, "...the doses found to be most effective are around two orders of

magnitude, or 100 times, higher that the maximum dose recommended by **Cummins**." Another point of departure from **Cummins** is discussed by **Dr. Wolinsky** on page 4 of his Rule 1.132 Declaration:

> Particularly important is Applicant's demonstration of an unusual dose-response relationship for oral administration of type one interferons to have any effect. It is meticulously demonstrated that both doses that are too low and doses that are too high lack any clinical benefit in animal models of human autoimmune disease... Applicant's work thus defines a likely range of doses of type one oral interferons that would be clinically efficacious in humans with multiple sclerosis, rheumatoid arthritis and other inflammatory autoimmune diseases.

No such relationship is discussed in Cummins.

In the Office Action of October 23, 1998, the Examiner contends that the rejected claims do not contain the limitations on which the applicant has based his arguments. The applicant points out that claim 4 specifically refers to a dosage of from about 50 I.U./kg to about 25,000 I.U./kg. While the preferred dosages are not listed in the claims, these can be obtained from the specification and fall within the range listed in claim 4.

In reference to the described dosage regimen, the Examiner cites col. 5, lines 50-55 of **Cummins** which states:

> Daily dosage of interferon can be administered as a single dose or, preferably, it is divided and administered in a

multiple-dose daily regimen. A staggered regimen, for example one to three days of treatment per week or month, can be uses as an alternative to continuous daily treatment." (Emphasis added).

The Examiner contends that this anticipates the every other day administration of interferon described in the instant application. The Applicant respectfully disagrees. The first portion teaches a multiple-dose daily regimen rather than an alternate day regimen. In the second section, the spacing of the one to three days of treatment per week or month is not discussed and the **Cummins** patent is therefore non-enabling in that regard.

In the office action of October 23, 1998 (Page 6), the examiner states that the Examiner does not understand the Applicant's pointing out of Col. 6, lines 50-55 of **Cummins**. The applicant would like to point out that it was the Examiner who first cited this section in the 35 U.S.C. §102(b) rejection of the claims and the Applicant was merely responding to this. The Applicant notes that an alternate day dosage is not specifically mentioned in this citation. Furthermore, no claims are made in **Cummins** regarding the dosage schedule.

Thus, the applicant maintains that such substantial differences exist between the method of **Cummins** and the claims

presented in the instant application that the **Cummins** patent fails to anticipate the current claims. Therefore, based on the arguments herein and in the two Declarations under 37 CFR 1.132, the applicant respectfully requests that the rejection of claims 1-4 and 6 under 35 U.S.C. §102(b) as anticipated by **Cummins** be withdrawn.

The 35 U.S.C. §103 Rejections

Claims 5 remains rejected under 35 U.S.C. §103 as obvious over **Cummins, Jr.** (U.S. Patent 5019382). The Examiner specifically cites Col. 5, lines 50-55 as suggesting an alternating day dosage regimen. The applicant respectfully disagrees.

The appropriate section of **Cummins** has be quoted *supra*. The section refers to a multiple-dose daily regimen rather than an alternate day regimen. While a regimen of one to three days per week or month is discussed, this is alluded to as a less preferred mode of administration by **Cummins**. In addition, the specific spacing of the treatment is not discussed. It is unclear whether this section refers to three continuous days on treatment followed by a period of day without treatment or whether it refers to single days of treatment separated by days without treatment. As such, the section is non-enabling and does not render claim 5

obvious. Therefore, the applicant respectfully requests that the rejection of claim 5 under 35 U.S.C. §103 as obvious over **Cummins** be withdrawn.

Claims 1-18 remain rejected under 35 U.S.C. §103 as obvious over **Cummins, Jr.** (U.S. Patent 5019382) in view of **Shibutani** et al. (Iyakuhin Kenkyu, vol . 18(4), pp. 571-82, 1987) and further in view of **Sobel** (abstracts of WO 94/20122 or U.S. Patent 5,624,895). The applicant respectfully disagrees.

The **Sobel** abstract describes methods of treating "an asymptomatic preclinical autoimmune state in a mammal" and inhibiting "rejection of transplanted islet cells or a pancreas in a mammal." These methods do not pertain to the instant invention.

The **Sobel** patent (U.S. Patent 5,624,895) was issued on April 29, 1997. The instant application is a continuation in part which claims priority back to several applications filed before this date as noted on page 1, lines 11-17:

> This application is a continuation-in-part of application serial number 08/844,731 filed April 21, 1997, which is a continuation of application serial number 08/631,470, filed April 12, 1996, which was a continuation-in-part of application serial number 08/408,271, filed March 24, 1995, which was a continuation-in-part of application serial number 08/226,631, filed April 12, 1994.

Thus, since the **Sobel** patent was not available at the time the instant invention was made, it is not a valid reference under 35 U.S.C. §103 for the rejection of claims 1-18. Nevertheless, the **Sobel** patent's description of the use of interferon gamma to treat diabetes mellitus actually teaches away from the instant investigation. Pages 53 and 54 of the Applicant's specification describe that reduction of interferon gamma levels following administration of type I interferons (alpha and/or beta) may in some way ameliorate the severity of the autoimmune disease:

> At day 13 after immunization, in situ IFN-γ production was reduced together with inflammation... **In combination, the present invention demonstrates that oral administration of IFN-α/β reduces the severity of experimental allergic neuritis by a reduction in IFN-γ production**... Parenteral IFN-γ administration has been shown to augment both myelin-induced and T-cell mediated experimental allergic neuritis... while the opposite effect was obtained by parenteral administration of anti-IFN-γ antibody... Decreased IFN-γ and inflammation in early stages and diminished demyelination at later stages of disease suggest a critical role for IFN-γ in the pathogenesis of experimental allergic neuritis. (emphasis added).

In contrast, the **Sobel** patent teaches the 'surprising' therapeutic application of IFN-γ for autoimmune diabetes. Also, as explained in both of the Rule 1.132 Declarations, simply because gamma

interferon is also an interferon does not mean that its potential use renders the application of a different class of interferons obvious.

The **Shibutani** abstract describes the lack of toxicity of high doses of human beta interferon in mice and rats. It by no means teaches or suggests a method of oral administration of a type one interferon in the treatment of autoimmune diseases. In addition, the lack of toxicity of higher doses does not imply that those doses would be efficacious in the treatment of autoimmune diseases, and further undue experimentation would be necessary to determine if higher doses would indeed be useful in the treatment of a particular disease. The addition of the **Sobel** references to **Cummins** and **Shibutani** fails to make the instant invention obvious.

In the Rule 1.132 declarations, the issue of dosage is described in some detail. The instant application is precise and meticulous in its delineation of a dose-response relationship for oral administration and ingestion of type one interferons. This relationship is somewhat exceptional. No overlap exists in the dosages used by **Cummins** and the doses found to most effective in the present invention which are about two order of magnitude greater than those used by **Cummins**. As pointed out by **Dr.**

Wolinsky, the Applicant has "meticulously demonstrated that both doses that are too low and doses that are too high lack any clinical benefit." One skilled in art would not be able to determine this from the combination of **Cummins** and **Shibutani** and the **Sobel** references without extensive, undue experimentation.

In addition, as described *supra*, the higher dose regimen is only one of several differences between **Cummins** and the present application. The differences in route of administration, dosage regimen, and degree of clinical enablement have already been discussed in depth previously herein. The human clinical data in the **Cummins** specification is highly anecdotal and non-enabling. A person having ordinary skill in the art would not be likely to believe **Cummins**' rhetoric regarding the importance of contact with the oropharyngeal membranes nor would such a person be motivated to make the instant application based on this work. These deficiencies are not resolved by the addition of the **Shibutani** and **Sobel** references.

In reference to the combination of **Cummins**, **Shibutani**, and **Sobel**, **Dr. Lindsey** writes:

> Clearly, one with ordinary skill in the art of autoimmune pathophysiology and treatment would not expect clinical efficacy in humans from the oral administration of alpha interferon after having read the **Cummins** and the **Shibutani**

> et al. ... and **Sobel** references. In fact, the opposite expectation that ingesting interferon would have no effect is more reasonable. Interferon is a protein, and proteins are broken down in the gastrointestinal tract. Thus, a person having ordinary skill in this art would expect interferon to be inactive when swallowed. Hence, the claimed methods not only are not obvious to one of ordinary skill, they are also counterintuitive.

On this same point, Dr. Wolinsky writes, "One would, if anything, expect such administration to have no clinical effect... any person with ordinary skill in this art would expect interferons to be biologically inert after being swallowed."

On page 6 of the Office Action mailed October 23, 1998, the Examiner argued that the Applicant has improperly criticized the references individually instead of what the combination of the references would suggest to one skilled in the art. The Applicant respectfully disagrees.

The many deficiencies in **Cummins** relative to the instant invention have been discussed in depth *supra*. These deficiencies are not resolved by the addition of the **Shibutani** and **Sobel**'s U.S. Patent 5,624,895 and abstract WO 94/20122. While **Shibutani** indicates that a higher dosage is nontoxic, it does not suggests that oral administration and ingestion of such a higher dosage would be effective in the treatment of diabetes mellitus. These combined deficiencies are not resolved by the addition of the

Sobel references. U.S. Patent 5,624,895 makes no suggestion in relationship to the other references because it describes results obtained with an entirely different class of interferon and actually teaches away from some of the observations of the current application. The WO 94/20122 abstract does discuss the treatment of a preclinical autoimmune state but does specify which autoimmune conditions were treated. Likewise, the mechanism which prevented the rejection of the transplanted islet cells is indeterminate. From the abstract, it cannot be ruled out that this may occur by the inhibition of host rejection of allogeneic and xenogeneic tissue grafts.

In conclusion, no combination of the cited references would enable one having ordinary skill in the art to create the instant invention. Accordingly, the applicant respectfully requests that the rejection of claims 1-18 under 35 U.S.C. §103 as obvious over **Cummins** in view of **Shibutani**, further in view of **Sobel** (abstracts of WO 94/20122 or U.S. Patent 5,624,895) be withdrawn.

Objections to the Sequence Listing

Sequence Listing was submitted previously but could not be processed by the Scientific and Technical Information Center

(STIC) as a result of errors in lines <211> of sequences 1 and 5 in relation to the number of nucleotide present, in the formatting of sequences 1 and 5, and in the presence of extraneous material at the end of the file. The Applicant submits herewith a new Sequence Listing and Disk correcting these errors. The Applicant respectfully requests that the objection to the Sequence List be withdrawn.

The 35 U.S.C. §101 Rejections

Claims 1-7 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as claims 1-7 of copending application Serial No. 08/631470. If either application be allowed, the Applicant will cancel the appropriate claims or submit a terminal disclaimer. In the meantime, Applicant respectfully requests that the 35 U.S.C. §101 rejection of claims 1-7 be held in abeyance.

Claims 1-18 are rejected under 35 U.S.C. §101 as claiming the same invention as claims 1-18 of copending application Serial No. 08/844731. If either application be allowed, the Applicant will cancel the appropriate claims or submit a terminal disclaimer. In the meantime, Applicant respectfully requests that the 35 U.S.C. §101 rejection of claims 1-18 be held in abeyance.

Obviousness-Type Double Patenting

Claims 8-18 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 8-18 copending application Serial No. 08/631470 in view of the abstracts of WO 94/20122, Gross et al. and Giron et al. Should either application be allowed, the Applicant will submit a terminal disclaimer in a timely manner. In the meantime, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 8-18 be held in abeyance.

This is intended to be a complete response to the Final Office Action mailed March 25, 1999. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: April 29, 1999

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